Remarks

Claims 1-3, 5-10, 13-33, 35-41 and 66-67 are pending. Upon entry of this amendment, claims 16, 18, 19 are cancelled without prejudice to prosecution in a future application. Claims 68-70 are added. Therefore, claims 1-3, 5-10, 13-15, 17, 20-33, 35-41 and 66-70 are now pending.

Support for the claim amendments and new claims can be found throughout the specification, for example:

Claim 1: original claim 16, page 17, lines 1-10, page 27, line 33- page 28, line 1;

Claims 2, 8, 13, and 66: page 17, lines 1-10 and 21-31; page 27, line 33- page 28, line 1

Claims 35 and 68: page 25, line 13.

Claims 69-70: page 11, lines 3-7.

No new matter is introduced by these amendments, and no amendments were made to distinguish prior art.

35 U.S.C. § 112, first paragraph: written description

Claims 1-3, 5-10, 13-33, 35-41 and 66-67 remain rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. Applicants disagree and request reconsideration.

It is well settled that "[t]he test for determining compliance with the written description requirement is whether the disclosure of the application as originally filed reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter ..." *In re Kaslow*, 217 USPQ 1089, 1096 (Fed. Cir. 1983).

As set forth in Federal Circuit decisions, a specification complies with the written description requirement if it provides "a precise definition, such as by structure, formula, chemical name, or physical properties of the claimed subject matter sufficient to distinguish it from other materials." See, e.g., *University of California v. Eli Lilly and Co.*, 43 U.S.P.Q.2d 1398, 1404 (Fed. Cir. 1997); *Enzo Biochem v. Gen-Probe Inc.*, 63 U.S.P.Q.2d 1609, 1613 (Fed. Cir. 2002).

It is asserted that Applicants have not shown any other type of cell transformed with any

other beta-alanine aminotransferase comprising up to 10% variation relative to the specific sequence of SEQ ID NO: 20 wherein said sequence is transformed into any cell type. Although Applicants continue to disagree for the response recited in the previous response of March 30, 2009, in order to expected prosecution, the claims have been amended.

First, the cell type has been amended to recite prokaryotic cells. Other cell types have been cancelled (*e.g.*, claims 18 and 19). Methods of generating the appropriate nucleic acid molecules and transforming such into prokaryotic cells are well known in the art, and are described in the specification (see for example see page 26, line 32 – page 31, line 2 and Example 8). In addition, specific examples of transformed prokaryotic cells are provided in the Examples section (see Examples 4-7). As the specification provides specific examples of prokaryotic cells that can be used, adequate written description is provided for transformed prokaryotic cells.

Second, the % sequence identity has been increased to 95%. As noted previously, Applicants have identified two separate beta-alanine/pyruvate aminotransferases having only 76.6% sequence identity at the protein level. The Office concludes that various proteins that may have common sequences may not be functional equivalents (see for example introduction in Haft *et al.*, *Nucleic acid Res,* 2001, 29:41-43). However, Applicants are not claiming non-functional variants, as the claim specifies that the variant sequence "is capable of producing malonate semialdehyde and alanine from beta-alanine and pyruvate." Thus, the claim provides a functional limitation, such that non-functional equivalents are disclaimed.

The Federal Circuit provides that the written description requirement for a genus of DNAs is met by a recitation of a representative number of DNAs, defined by nucleotide sequence, falling within the scope of the genus or by a recitation of structural features common to the members of the genus.

It is well established in the art that the definition of a genus of genes encoding polypeptides having an enzyme activity of interest is accomplished by using structural features that show the relatedness of the genes and their encoded products. For decades the scientific community has employed three structural features to define the relatedness of genes and their products. The three structural features are (1) percent identity of the amino acid sequences encoded by the genes, (2) percent identity of the nucleic acid sequences of the genes, and (3) nucleic acid hybridizations under defined stringent conditions to identify complementary strands of genes

encoding the same or similar enzyme or protein function.

In the claims at issue, Applicants provide a recitation of three structural features common to the claimed genus: (1) a polypeptide comprising an amino acid sequence having at least 95% sequence identity SEQ ID NO: 20; (2) a polypeptide that is encoded by a polynucleotide that hybridizes under at least high stringency conditions with SEQ ID NO: 19, (3) a polypeptide that is encoded by the nucleic acid sequence comprising SEQ ID NO: 19, or (4) a polypeptide encoded by a polynucleotide comprising a nucleotide sequence having at least 95% sequence identity with SEQ ID NO: 19. The structural features are described throughout the specification, for example on page 21, line 28, to page 22, line 3, and page 27, line 13 to page 30, line 10, of the specification.

The three structural features of percent identity at the deduced amino acid sequence level, percent identity at the DNA level, and the ability of the claimed nucleic acid sequence to hybridize under specific stringency conditions have been used to predict the function of polypeptides encoded by novel genes, and to place them in an existing genus. The scientific literature abounds with disclosures of these three structural features to describe the relatedness of proteins and their genes as well as to distinguish a protein and its gene from other proteins and their genes. Percent identity is highly predictive of protein function and without this tool it would be impossible to make meaningful annotations of genomes in sequencing projects. Proteins that share 95% amino acid identity are known to possess the same catalytic/biochemical function which has formed the basis for genome annotation and comparative genomics. In fact, 95% identity is an extremely conservative criterion for judging functional similarity.

The USPTO's Written Description Guidelines describes two examples, Examples 9 and 14, which are applicable to the instant claims.

Example 9 discloses an example for claiming nucleic acids using hybridization language, which is pertinent to the claims of the present invention: "An isolated nucleic acid that specifically hybridizes under highly stringent conditions to the complement of the sequence set forth in SEQ ID NO: 1, wherein said nucleic acid encodes a protein that binds to a dopamine receptor and stimulates adenylate cyclase activity." The instant claims recite in part: "wherein the exogenous nucleic acid molecule encoding the beta-alanine/pyruvate aminotransferase comprises a sequence that can hybridize under highly stringent hybridization conditions to SEQ ID NO: 19." One skilled in the art would not expect substantial variation among species

encompassed within the scope of the claims because the highly stringent hybridization conditions recited in the claim yield structurally similar DNAs. As the Written Description Guidelines provide, a representative number of species is disclosed, since highly stringent hybridization conditions in combination with the coding function of DNA and the level of skill and knowledge in the art are adequate to determine that Applicants were in possession of the claimed invention.

Example 14 discloses an example for claiming protein variants using percent identity language, which is also pertinent to the claims of the present invention: "A protein having SEQ ID NO: 3 and variants thereof that are at least 95% identical to SEQ ID NO: 3 and catalyze the reaction of A - B.". The instant claims recite in part: "a beta-alanine/pyruvate aminotransferase having at least 95% sequence identity to SEQ ID NO: 20". Procedures for making variants of SEQ ID NO: 20 are conventional in the art and an assay is described in the specification that will identify other proteins having the claimed beta-alanine/pyruvate aminotransferase activity. Moreover, procedures for making variants of SEQ ID NO: 20 that have 95% identity to SEQ ID NO: 20 and retain beta-alanine/pyruvate aminotransferase activity are conventional in the art. The genus of proteins that are variants of SEQ ID NO: 20 do not have substantial variation since all of the variants must possess the specified beta-alanine/pyruvate aminotransferase activity (*e.g.*, producing malonate semialdehyde and alanine from beta-alanine and pyruvate) and must have at least 95% identity to the reference sequence, SEQ ID NO: 20. The disclosed species of SEQ ID NO: 20 is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an enzyme assay, which Applicants provided for identifying all of the at least 95% identical variants of SEQ ID NO: 20 that have beta-alanine/pyruvate aminotransferase activity. As the Written Description Guidelines provide, one skilled in the art would conclude that Applicants were in possession of the necessary common attributes possessed by the members of the genus.

It is asserted on page 5 of the Office action that applicants' assert that deletion of lactate dehydrogenase, the enzyme that catalyzes the formation/interconversion of lactic acid and pyruvate in *E. coli*, results in elimination of lactic acid formation, hence is *advantageous* for the detection of the formation of 3-HP because of the similarity in structure and chromatographic behavior of lactic acid and 3-HP (emphasis added). From this statement the Office concludes that this deletion mutant is useful to distinguish 3-HP that is produced since the chromatographic

behavior between lactic acid and 3-HP is not distinguishable, and thus strains without deletion of lactate dehydrogenase are indistinguishable from strains that only produce lactic acid. Applicants disagree with this conclusion. The specific example provided in the specification is merely one method that can be used to distinguish between lactic acid and 3-HP. Other methods are well known in the art. For example, Ross *et al.* (*Anal. Chem.*, 79:4840-44, 2007, copy enclosed), provide a method for quantification of organic acids using ultraperformance liquid chromatography/electrospray-tandem mass spectrometry. This method permits separate detection of lactic acid and 3-HP without chromatographic separation (see FIG. 1). Thus strains without deletion of lactate dehydrogenase are encompassed by this invention as they are distinguishable from strains that only produce lactic acid (for example by detecting the presence of the transgenic nucleic acid sequence). Applicants note that claim 67 recites that the cells do not express lactate dehydrogenase.

For the foregoing reasons, Applicants submit that the written description rejections under 35 U.S.C. § 112, first paragraph have been overcome and respectfully request reconsideration and withdrawal of the rejection.

35 U.S.C. § 112, first paragraph: enablement

Claims 1-3, 5-10, 13-33, 35-41 and 66-67 remain rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. Applicants disagree and request reconsideration.

It is asserted that the scope of the claims are not commensurate with the enablement provided by the disclosure with regards to the extremely large number of cell types and nucleic acids that encode the various enzymes broadly encompassed in the claims. As discussed above, the claims are amended to recite that the cells are prokaryotic cells. Applicants have shown that 3-HP can be expressed in *E. coli* by expressing exogenous beta-alanine/pyruvate aminotransferase and alanine 2,3-aminomutase. One skilled in the art would expect similar results with other prokaryotic cells, and the Office has not provided any contrary evidence that such would not be expected. Therefore, the specification is enabled for the use of prokaryotic cells.

The Office concludes that various proteins that may have common sequences may not be

functional equivalents (see for example introduction in Haft *et al.*, *Nucleic acid Res,* 2001, 29:41-43). However, as noted above, Applicants are not claiming non-functional variants, as the claim specifies that the variant sequence "is capable of producing malonate semialdehyde and alanine from beta-alanine and pyruvate." Thus, the claim provides a functional limitation, such that non-functional equivalents are disclaimed. Second, the % sequence identity has been increased to 95%. As noted previously, Applicants have identified two separate beta-alanine/pyruvate aminotransferases having only 76.6% sequence identity at the protein level, and shown that both in combination with alanine 2,3-aminomutase can permit a prokaryotic cell to express 3-HP. Thus, the claims are enabled for their scope.

The Office also concludes that a host cell that does not comprise a deletion of lactate dehydrogenase may produce lactic acid that is indistinguishable from 3-HP. As noted above, the specific example provided in the specification is merely one method that can be used to distinguish between lactic acid and 3-HP. Other methods are well known in the art. For example, Ross *et al.* (*Anal. Chem.*, 79:4840-44, 2007, copy enclosed), provide a method for quantification of organic acids using ultraperformance liquid chromatography/electrospray-tandem mass spectrometry. This method permits separate detection of lactic acid and 3-HP without chromatographic separation (see FIG. 1). Thus strains without deletion of lactate dehydrogenase are enabled as they are distinguishable from strains that only produce lactic acid (for example by detecting the presence of the transgenic nucleic acid sequence).

For the foregoing reasons, Applicants submit that the enablement rejections under 35 U.S.C. § 112, first paragraph have been overcome and respectfully request reconsideration and withdrawal of the rejection.

Examination of Additional Species

As generic claim 1 is now in condition for allowance, Applicants request consideration of claims to the non-elected species (including SEQ ID NOS: 17, 21 and 23) as per 37 C.F.R. § 1.141.

As the claims are in condition for allowance, entry of this Amendment and a Notice of Allowance is requested. If there are any questions regarding this response, the Examiner is invited to telephone the undersigned.

Respectfully submitted,

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